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Case report

Neurological sequelae in patients recovered from fulminant hepatic failure

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SUMMARY Two teenage patients with fulminant hepatic failure progressing to grade 4 encephalopathy with clinical signs of cerebral oedema are described, in whom permanent neurological injury (involving the brain stem in one and the cerebral cortex in the other) was the sequel to an otherwise full recovery. The present day management of cerebral oedema may, as in these two cases, ensure the survival of patients with fulminant hepatic failure who would previously have been likely to die from the effects of raised intracranial pressure. As a result it is now possible more recovered cases will be seen with residual neurological deficits, a previously very rarely recorded event.

Patients who recover from fulminant hepatic failure usually do so completely[1] and this applies both to the return of normal liver histology[2] and the recovery of secondarily affected organs such as the brain. In 1974, however, Fiasse *et al* described one patient who was dysphasic for many months after recovery from fulminant viral hepatitis[3] while in 1977 we reported the occurrence of permanent cortical and optic atrophy in a young women after acetaminophen induced fulminant hepatic failure.[4] In the present paper we describe localised neurological deficits and persisting neurological sequelae in two further patients with fulminant hepatic failure after severe (grade 4) hepatic encephalopathy complicated by clinical evidence of recurrent and life threatening cerebral oedema.

Case histories

A previously healthy 17 year old boy (SC) sought medical attention 72 hours after an overdose of 20–30 tablets of paracetamol (acetaminophen). Prothrombin time was prolonged to 120 seconds (control 13) and the patient was therefore transferred to the Liver Failure Unit, KCH later that day. On arrival he was slightly drowsy although cooperative and orientated – grade 1 encephalopathy. Over the subsequent 18 hours he became increasingly confused and somnolent. Signs of brain stem dysfunction appeared with poorly reacting pupils, paroxysmal hypertension and decerebrate posturing. Despite the institution of artificial liver support using charcoal haemoperfusion there was a rapid deterioration into a state of deep grade 4 hepatic coma. At 24 hours fixed dilated pupils and severe opisthotonus preceded the onset of a respiratory arrest. Immediate intubation, mechanical hyperventilation and a 100 ml intravenous bolus of 20% mannitol corrected the pupillary and postural abnormalities. There was further clinical evidence of severe and recurrent cerebral oedema over the next three days as evidenced by periods of hypertension (maximally 190/90 mm Hg) accompanied by dilated and at times unreactive pupils. On occasions when hypertension was sustained for longer than two minutes and/or unequal or poorly reactive pupils appeared, rapid intravenous infusion of 50–100 ml hypertonic mannitol (total required 400 ml per day: maximum 200 ml in one hour) combined with passive fluid ultrafiltration, 150–300 ml over 30 mins, necessary because of oliguric renal failure, was successful in stabilising his blood pressure and restoring normal pupillary responses. On the seventh day the patient regained consciousness when his prothrombin time, which had been steadily

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falling since his transfer, was 13 seconds. After weaning from ventilatory support hitherto unsuspected cranial nerve and limb weakness was noted. Examination showed a left sided third nerve palsy resulting in complete ptosis and ocular divergence, minimal left sided facial weakness and loss of voluntary and reflex movement of the left palate. An ipsilateral spastic hemiparesis of moderate severity affecting mainly the upper limb was also present. A computerised axial tomogram (1010 EMI scanner) of the brain revealed no visible lesion. Although some improvement in these neurological abnormalities was seen over the subsequent three months, mild arm weakness and an inability to fully adduct the left eye persisted.

PR, a 19 year old man, experienced abdominal pain and vomiting two days after selfinjecting amphetamines. He admitted abusing heroin and amphetamines, the latter often in doses of 1 g or more per day, for three years. On admission to his local hospital the patient was found to have an enlarged tender liver, an aspartate transaminase level >450 IU/l, a prolonged prothrombin time and hepatitis B surface antigenaemia (subsequently shown to be IgM anti-HBc positive, Delta IgM antibody negative). There was no clinical or bacteriological evidence of infective endocarditis and neurological examination was normal. Two days later he had become confused and aggressive and was transferred to the Liver Failure Unit unrousable (grade 4 encephalopathy) with a prothrombin time of 93 seconds. On arrival the patient was started on charcoal haemoperfusion for a single 10 hour period and mechanical ventilation instituted because of respiratory distress and developing anoxia (PO_2 8·4 kPA, PCO_2 2·9 kPa), there being radiographic evidence of lower lobe pulmonary consolidation. In addition renal haemodialysis was required because of established anuria.

Twenty four hours after the patient's transfer the right pupil suddenly dilated and became unreactive. Paroxysms of hypertension, not exceeding 200/110 mm Hg, were also recorded. Hypertonic mannitol combined with fluid ultrafiltration was successfully used as before on this and two other occasions over the succeeding five days in volumes of 50 ml and 50 and 200 ml respectively to restore a normal reaction to light in previously fixed and dilated pupils. After seven days coma lightened and evidence was revealed of marked left sided weakness and sensory loss.

Examination of the cranial nerves at review five months later revealed persisting left sided visual inattention, reduced sensation over the three divisions of the left trigeminal nerve, a subjectively impaired left corneal reflex, upper motor neurone type facial weakness and reduced shrugging of the left shoulder. Peripherally an abnormal posture of the left hand with flexed fingers was noted. Tone in the arm was increased and the tendon reflexes were pathologically brisk. Distally there was mild weakness of the left arm but only minimal weakness of the left leg. Joint position sense was grossly impaired in the left arm but not the left leg. All other sensory modalities were less severely impaired, the left arm again being more severely affected than the left leg. Gait was normal apart from the abnormal posture of the left hand. A computed tomography brain scan showed a mature infarct in a right middle cerebral artery distribution. Digital subtraction angiography of the cerebral vessels excluded major vessel obstruction but did reveal narrowing and irregularity of the right middle cerebral artery.

Discussion

Cerebral oedema is a frequent[5] and often fatal complication of severe fulminant hepatic failure, being found in approximately 50–80% of all cases coming to necropsy.[6 7] Its presence and determining influence upon survival are most dramatically apparent when there occurs acute brain stem dysfunction and sudden neurological deterioration. Manometric studies have shown these events are preceded by a precipitous rise in intracranial pressure which, if untreated by the rapid intravenous infusion of hypertonic mannitol, inevitably results in the uncal or tentorial herniation.[8 9] Concomitant interruption of the vascular supply to vital brain stem structures is therefore the most likely explanation why patients with fulminant hepatic failure who sustain cerebral oedema related neurological injury so rarely survive. In the only possible exception we have previously seen,[4] and already referred to, gross visual field constriction in keeping with damage to the occipital cortex was a permanent feature. Widespread cerebral atrophy was also a sequel, however, and the possibility that the lesions were mainly caused by cerebral anoxia after an earlier cardiac arrest could not be excluded. In the present case 1, who also risked anoxic damage, localised brain stem injury after signs of acute relapsing brain stem dysfunction suggests this injury was much more likely to have been because of the compressive effects of severe and prolonged cerebral oedema. As the onset of signs of brian stem dysfunction, in particular impaired pupillary responses, has recently been shown to be a reliable indicator of cerebral oedema requiring treatment,[10] we no longer directly measure intracranial pressures in patients with acute liver failure. The severity of the cerebral oedema in this case, however, can be inferred from the

patient's respiratory arrest, an occurrence previously documented as only after a very marked and sustained rise in intracranial pressure and which is often the first indication in these patients of fatal brain stem coning.[9]

In case 2, who also required urgent treatment for signs of severe cerebral oedema and incipient brain stem coning, infarction as shown by computed tomography scanning in fact occurred in an area supplied by the middle cerebral artery. This is surprising as the supratentorial position of this vessel does not render it vulnerable to compression when the effect of raised intracranial pressure is to displace the brain caudally.[11] A more likely possibility therefore, and favoured by the abnormal narrowing of the middle cerebral artery seen on the patient's angiogram, is that cerebral oedema, by critically reducing cerebral perfusion pressure and therefore cerebral blood flow,[12] may have precipitated infarction in the territory supplied by an already damaged cerebral artery. Damage in this instance may have resulted from the abuse of intravenously administered drugs in particular large quantities of amphetamines which have been implicated in the development of a chemically induced necrotising angiitis that may affect mesentric[13] or cerebral vessels.[14] Angiographic changes in these latter cases and consistent with those visible in this patient include irregular segmental areas of constriction with changes of calibre and contour of the vessel walls of large or interval size arteries.[14]

As illustrated, the current management of life threatening cerebral oedema with mannitol (and fluid ultrafiltration if urine is not produced) undoubtedly rescues many patients with fulminant hepatic failure who would otherwise die of this complication. Our recent experience would suggest such success may also be reflected by an increase in the number of those surviving with cerebral oedema related neurological sequelae.

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